Search Strategy

FILE 'USPATFULL' ENTERED AT 14:20:27 ON 27 JUN 2001

		E	ALLAWAY GRAHAM P/IN
L1	5	S	E3
		E	LITWIN VIRGINIA M/IN
L2	2	S	E3
L3	1	S	L2 NOT L1
		E	MADDON PAUL J/IN
L4	14	S	E3
L5	9	S	L4 NOT (L1 OR L2)
		E	OLSON WILLIAM C/IN
L6	2	S	E3
L7	16	S	(INHIBITION OF HIV-1 INFECTIVITY OR INHIBITION OF HIV-1 FUSIO
L8	2	S	L7 AND (CHEMOKINE OR CCR5 OR CXCR4)
L9	14	S	L7 NOT L8
L10	12652	S	(HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L11	8423	S	L10 AND (ANTIVIRAL? OR INHIBITOR? OR ANTAGONIST?)
L12	202	S	L11 AND (CHEMOKINE OR CCR5 OR CXCR4)
L13	77	S	L12 AND (INHIBIT? (10W) FUSION OR INHIBIT? (10W) INFECTI?)
L14	20	S	L11 AND (FUSION INHIBITOR?)
L15	125	S	L12 NOT (L13 OR L14)

FILE 'MEDLINE' ENTERED AT 15:01:20 ON 27 JUN 2001

		E	ALLAWAY G P/AU
L16	21	S	E3
		E	LITWIN V M/AU
L17	10	S	E1
		E	MADDON P J/AU
L18	35	S	E3
L19	25	S	L18 NOT (L16 OR L17)
		E	OLSON W C/AU
L20	22	S	E3
L21	12	S	L20 NOT (L16 OR L17 OR L18)
L22	104081	S	(HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L23	20	S	L22 AND (SMALL-MOLECULE INHIBITOR?)
L24	10	S	L23 AND (CHEMOKINE OR CCR5 OR CXCR4)
		E	DRAGIC T/AU
L25	22	S	E3
L26	2	S	L25 AND TAK-779
L27	20	S	L25 NOT L26
L28	11	S	L22 AND (TAK-779)
L29	15	S	L22 AND (T-134 OR T-22 OR ALX40-4C OR CGP64222)

L1 ANSWER 2 OF 5 USPATFULL
2000:109525 Method for preventing HIV-1 infection of CD4.sup.+ cells.
Allaway, Graham P. , Mohegan Lake, NY, United States
Litwin, Virginia M., Fayetteville, NY, United States
Maddon, Paul J., Elmsford, NY, United States
Olson, William C., Ossining, NY, United States
Progenics Pharmaceuticals, Inc., Tarrytown, NY, United States (U.S. corporation)
US 6107019 20000822
APPLICATION: US 1997-876078 19970613 (8)
PRIORITY: US 1996-19715 19960614 (60)
US 1996-14532 19960402 (60)
DOCUMENT TYPE: Utility.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention provides methods for inhibiting fusion of HIV-1 to CD4.sup.+ cells which comprise contacting CD4.sup.+ cells with a non-chemokine agent capable of binding to a chemokine receptor in an amount and under conditions such that fusion of HIV-1 to the CD4.sup.+ cells is inhibited. This invention also provides methods for inhibiting HIV-1 infection of CD4.sup.+ cells which comprise contacting CD4.sup.+ cells with a non-chemokine agent capable of binding to a chemokine receptor in an amount and under conditions such that fusion of HIV-1 to the CD4.sup.+ cells is inhibited, thereby inhibiting the HIV-1 infection. This invention provides non-chemokine agents capable of binding to the chemokine receptor and inhibiting fusion of HIV-1 to CD4.sup.+ cells. This invention also provides pharmaceutical compositions comprising an amount of the non-chemokine agent capable of binding to the chemokine receptor and inhibiting fusion of HIV-1 to CD4.sup.+ cells effective to prevent fusion of HIV-1 to CD4.sup.+ cells and a pharmaceutically acceptable carrier.

CLM What is claimed is:
1. An in vitro method for determining whether an agent is capable of inhibiting HIV-1 infection of a CD4.sup.+ cell susceptible to HIV-1 infection comprising the steps of: (a) fixing a chemokine receptor on a solid matrix wherein the chemokine receptor is a co-receptor for HIV-1 infection; (b) contacting the fixed chemokine receptor with the agent under conditions permitting binding of the agent to the chemokine receptor; (c) removing any unbound agent; (d) contacting the resulting fixed chemokine receptor to which the agent is bound with a predetermined amount of gp120/CD4.sup.+ complex under conditions permitting binding of gp120/CD4 .sup.+ complex to the fixed chemokine receptor in the absence of the agent; (e) removing any unbound gp120/CD4.sup.+ complex; (f) measuring the amount of gp120/CD4.sup.+ complex bound to the fixed chemokine receptor; and (g) comparing the amount measured in step (f) with the amount measured in the absence of the agent, a decrease in the amount bound in the presence of the agent indicating that the agent is capable of inhibiting HIV-1 infection.

2. An in vitro method for determining whether an agent is capable of inhibuting HIV-1 infection of a CD4.sup.+ cell susceptible to HIV-1 infection comprising the steps: (a) fixing a chernokine receptor on a solid matrix wherein the chemokine receptor is a co-receptor for HIV-1 infection; (b) contacting the fixed chemokine receptor with the agent and a predetermined amount of gp120/CD4.sup.+ complex under conditions permitting binding of the gp120/CD4.sup.+ complex to the fixed chemokine receptor in the absence of the agent; (c) removing any unbound agent or unbound gp120/CD4.sup.+ complex or both; (d) measuring the amount of gp120/CD4.sup.+ complex bound to the fixed chemokine

receptor; and (e) comparing the amount measured in step (d) with the amount measured in the absence of the agent, a decrease in the amount bound in the presence of the agent indicating that the agent is capable of inhibiting HIV-1 infection.

3. An in vitro method for determining whether an agent is capable of inhibiting HIV-1 infection of a CD4.sup.+ cell susceptible to HIV-1 infection comprising steps of: (a) fixing a gp120/CD4.sup.+ complex on a solid matrix; (b) contacting the fixed gp120/CD4.sup.+ complex with the agent under conditions permitting the binding of the agent to the gp120/CD4.sup.+ complex; (c) removing any unbound agent; (d) contacting the resulting fixed gp120/CD4.sup.+ complex to which the agent is bcund with a predetermined amount of chemokine receptor, wherein the chemokine receptor is a co-receptor for HIV-1 infection, under conditions permitting binding of the chemokine receptor to the fixed the gp120/CD4.sup.+ complex in the absence of the agent; (e) removing any unbound chemokine receptor; (f) measuring the amount of chemokine receptor bound to the fixed gp120/CD4.sup.+ ; and (g) comparing the amount measured in step (f) with the amount measured in the absence of the agent, a decrease in the amount bound in the presence of the agent indicating that the agent is capable of inhibiting HIV-1 infection.

4. An in vitro method for determining whether an agent is capable of inhibiting HIV-1 infection of a CD4.sup.+ cell susceptible to HIV-1 infection comprising steps of: (a) fixing a gp120/CD4.sup.+ complex on a solid matrix: (b) contacting the fixed gp120/CD4.sup.+ complex with the agent and a predetermined amount of chemokine receptor, wherein the chemokine receptor is a co-receptor for HIV-1 infection, under co)nditions permitting binding of the chemokine receptor to the fixed gp120/CD4.sup.+ complex in the absence of the agent; (c) removing any unbound agent or any unbound chemokine receptor or both: (d) measuring the amount of chemorkine receptor bound to the fixed gp120/CD4.sup.+ ; and (e) comparing the amount measured in step (d) with the amount measured in the absence of the agent, a decrease in the amount bound in the presence of the agent indicating that the agent is capable of inhibiting HIV-1 infection.

5. The method of claim 1, 2, 3, or 4 wherein the CD4.sup.+ is a soluble CD4.sup.+.

6. The method of claim 1, 2, 3, or 4 wherein the chemokine receptor is expressed on a cell.

7. The method of claim 6 wherein the cell is a L1.2 cell.

8. The method of claim 1 or 2, wherein the gp120, CD4.sup.+ or both are labeled with a detectable marker.

9. The method of claim 3 or 4 wherein the chemokine receptor is labeled with a detectable marker.

10. The method of claim 1 or 2, wherein the gp120, CD4.sup.+ or both are labeled with biotin.

11. The method of claim 2 or 4 wherein the chemokine receptor is labeled with biotin.

12. The method of any one of claims 1, 2, 3, or 4, wherein the chemockine receptor is CCR5.

L8 ANSWER 1 OF 2 USPATFULL

1999:96489 Methods and compositions for inhibiting HIV infection of cells by cleaving HIV co-receptor RNA.
Leavitt, Markley C., La Jolla, CA, United States
Tritz, Richard, San Diego, CA, United States
Feng, Yu, San Diego, CA, United States
Barber, Jack, San Diego, CA, United States
Yu, Mang, San Diego, CA, United States
Immusol Incorporated, San Diego, CA, United States (U.S. corporation)
US 5939538 19990817
APPLICATION: US 1996-770235 19961219 (8)
PRIORITY: US 1996-27875 19961025 (60)
DOCUMENT TYPE: Utility.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Methods of inhibiting HIV infection by blocking HIV co-receptor RNA expression are provided. Ribozymes which cleave HIV co-receptor RNA and inhibit HIV infection of cells are also provided. Co-receptor targets include fusin and CKR5.

L8 ANSWER 2 OF 2 USPATFULL
1998:58129 Phosphorothioate oligonucleotides that bind to the V3-loop and uses thereof.
Stein, Cy, New York, NY, United States
Lederman, Seth, New York, NY, United States
Sullivan, Gregory, New York, NY, United States
The Trustees of Columbia University in City of New York, New York, NY, United States (U.S. corporation)
US 5756710 19980526
APPLICATION: US 1996-658616 19960605 (8)
DOCUMENT TYPE: Utility.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides phosphorothioate oligonucleotide moieties comprising a phosphorothioate oligonucleotide comprising the sequence G.sub.m X.sub.n G.sub.p, wherein G is guanosine; X is thymidine, adenosine or cytidine, or a combination thereof; each of m, n and p is independently an integer greater than 2; the phosphorothioate oligonucleotide moiety being capable of binding to a V3 loop of HIV envelope glycoprotein. The invention further provides for a method of inhibiting HIV activity. The invention also provides for a method of inhibiting HIV activity in a subject. The invention further provides for a method of treating an HIV related disorder in a subject. Finally, the invention provides a pharmaceutical composition comprising a phosphorothioate oligonucleotide moiety and a pharmaceutically acceptable carrier.

L13 ANSWER 58 OF 77 USPATFULL
1999:75632 Substituted aminoquinolines as modulators of ***chemokine*** receptor activity.
Hagmann, William K., Westfield, NJ, United States
Springer, Martin S., Westfield, NJ, United States
Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)
US 5919776 19990706
APPLICATION: US 1997-993494 19971218 (8)
DOCUMENT TYPE: Utility.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention is directed to aminoquinolines of Formula I: ##STR1## (wherein R.sup.1, R.sup.2, R.sup.3, and R.sup.4 are defined herein) which are useful as modulators of ***chemokine*** receptor activity. In particular, these compounds are useful as modulators of the

chemokine receptors CCR-1, CCR-2, CCR-2A, CCR-2B, CCR-3, CCR-4, CCR-5, CXCR-3, and/or CXCR-4.

L13 ANSWER 68 OF 77 USPATFULL
1998:101499 Methods for screening of test compounds for inhibiting binding of a CD4- ***HIV*** 1 complex to a ***chemokine*** receptor.
Neurath, Alexander Robert, New York, NY, United States
Debnath, Asim Kumar, New York, NY, United States
Jiang, Shibo, Jackson Heights, NY, United States
Li, Yun-Yao, Flushing, NY, United States
Strick, Nathan, Oceanside, NY, United States
New York Blood Center, New York, NY, United States (U.S. corporation)
US 5798206 19980825
APPLICATION: US 1997-782044 19970110 (8)
DOCUMENT TYPE: Utility.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method for the screening of a test compound for inhibiting the binding of a CD4- ***HIV*** 1 complex to ***HIV*** -1 second receptors, comprising: (a) preparing a magnetic ligand by mixing a magnetic, CD4-containing substrate with ***HIV*** -1, (b) mixing the magnetic ligand from step (a) with a test compound, (c) adding cells that express the ***HIV*** -1 second receptors to the mixture from step (b), (d) separating cells with bound magnetic ligands from cells without bound magnetic ligands by contact with a magnetic separator, and (e) quantifying the cells with bound magnetic ligands and quantifying the cells without bound magnetic ligands.

L13 ANSWER 77 OF 77 USPATFULL
96:94576 Benzothiophene, benzofuran and indole-thiazepinones, oxazepinones and diazepinones as ***inhibitors*** of cell adhesion and as ***inhibitors*** of ***HIV*** .
Boschelli, Diane H., Plymouth, MI, United States
Connor, David T., Ann Arbor, MI, United States
Kramer, James B., Sylvania, OH, United States
Unangst, Paul C., Ann Arbor, MI, United States
Warner-Lambert Company, Morris Plains, NJ, United States (U.S. corporation)
US 5565446 19961015
APPLICATION: US 1995-444975 19950519 (8)
DOCUMENT TYPE: Utility.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Benzothiophene, benzofuran and indolethiazepinones, oxazepinones and diazepinones as well as methods of preparation thereof are described as agents which inhibit leukocyte adherence to vascular endothelium and, as such, are effective therapeutic agents for treating inflammatory diseases; these compounds also inhibit the activation of ***human*** ***immunodeficiency*** ***virus*** (***HIV***).

L13 ANSWER 28 OF 77 USPATFULL
2000:109525 Method for preventing ***HIV*** -1 infection of CD4.sup.+ cells .
Allaway, Graham P., Mohegan Lake, NY, United States
Litwin, Virginia M., Fayetteville, NY, United States
Maddon, Paul J., Elmsford, NY, United States
Olson, William C., Ossining, NY, United States
Progenics Pharmaceuticals, Inc., Tarrytown, NY, United States (U.S. corporation)
US 6107019 20000822
APPLICATION: US 1997-876078 19970613 (8)
PRIORITY: US 1996-19715 19960614 (60)

US 1996-14532 19960402 (60)
DOCUMENT TYPE: Utility.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention provides methods for ***inhibiting*** ***fusion*** of ***HIV*** -1 to CD4.sup.+ cells which comprise contacting CD4.sup.+ cells with a non- ***chemokine*** agent capable of binding to a ***chemokine*** receptor in an amount and under conditions such that fusion of ***HIV*** -1 to the CD4.sup.+ cells is ***inhibited*** . This invention also provides methods for ***inhibiting*** ***HIV*** -1 ***infection*** of CD4.sup.+ cells which comprise contacting CD4.sup.+ cells with a non- ***chemokine*** agent capable of binding to a ***chemokine*** receptor in an amount and under conditions such that fusion of ***HIV*** -1 to the CD4.sup.+ cells is ***inhibited*** , thereby ***inhibiting*** the ***HIV*** -1 ***infection*** . This invention provides non- ***chemokine*** agents capable of binding to the ***chemokine*** receptor and ***inhibiting*** ***fusion*** of ***HIV*** -1 to CD4.sup.+ cells. This invention also provides pharmaceutical compositions comprising an amount of the non- ***chemokine*** agent capable of binding to the ***chemokine*** receptor and ***inhibiting*** ***fusion*** of ***HIV*** -1 to CD4.sup.+ cells effective to prevent fusion of ***HIV*** -1 to CD4.sup.+ cells and a pharmaceutically acceptable carrier.

L13 ANSWER 24 OF 77 USPATFULL
2000:146384 ***Chemokine*** receptor ***antagonists*** .
Naya, Akira, Tsukuba, Japan
Owada, Yufu, Tsukuba, Japan
Saeki, Toshihiko, Tsukuba, Japan
Ohwaki, Kenji, Tsukuba, Japan
Iwasawa, Yoshikazu, Tsukuba, Japan
Banyu Pharmaceutical, Co., Ltd., Tokyo, Japan (non-U.S. corporation)
US 6140338 20001031
WO 9804554 19980205
APPLICATION: US 1999-147595 19990129 (9)
WO 1997-JP2548 19970723 19990129 PCT 371 date 19990129 PCT 102(e) date
PRIORITY: JP 1996-216019 19960729
JP 1996-336357 19961202
DOCUMENT TYPE: Utility.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to a compound of the general formula: ##STR1## wherein each of R.sup.1 and R.sup.2 which may be the same or different, is e.g. a hydrogen atom, a halogen atom or a lower alkyl group, X is an oxygen atom, a sulfur atom or CH, Y is CH or a nitrogen atom, and A is e.g. a 1-substituted-4-piperidinyl group, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable anion-exchange product thereof or a hydrate thereof. The compounds of the present invention have ***chemokine*** receptor antagonism, and thus they are useful as treating agents for various diseases relating to ***chemokine*** , such as acute inflammatory diseases, chronic inflammatory diseases, acquired immune deficiency syndrome, cancer, ischemic reflow disorder and/or arteriosclerosis.

L13 ANSWER 13 OF 77 USPATFULL
2001:4735 Pharmaceutical composition for antagonizing ***CCR5*** comprising anilide derivative.
Nishimura, Osamu, Hyogo, Japan
Baba, Masanori, Kagoshima, Japan
Sawada, Hidekazu, Osaka, Japan

Kanzaki, Naoyuki, Osaka, Japan
Kuroshima, Ken-ichi, Osaka, Japan
Shiraishi, Mitsuru, Hyogo, Japan
Aramaki, Yoshio, Hyogo, Japan
Takeda Chemical Industries, Ltd., Osaka, Japan (non-U.S. corporation)
US 6172061 B1 20010109
APPLICATION: US 1998-213377 19981217 (9)
PRIORITY: JP 1997-351480 19971219
JP 1998-218875 19980803
JP 1998-234388 19980820
US 1998-104847 19981016 (60)
US 1998-104845 19981016 (60)
DOCUMENT TYPE: Patent.

AB This invention is to provide a pharmaceutical composition for antagonizing ***CCR5*** which comprises a compound of the formula: ##STR1##

wherein R.sup.1 is an optionally substituted 5- to 6-membered ring; W is a divalent group of the formula: ##STR2##

wherein the ring A is an optionally substituted 5- to 6-membered aromatic ring, X is an optionally substituted C, N or O atom, and the ring B is an optionally substituted 5- to 7-membered ring; Z is a chemical bond or a divalent group; R.sup.2 is (1) an optionally substituted amino group in which a nitrogen atom may form a quaternary ammonium, etc., or a salt thereof.

L14 ANSWER 10 OF 20 USPATFULL
2000:12922 Isolated peptides derived from ***human*** ***immunodeficiency*** ***virus*** types 1 and 2 containing ***fusion*** ***inhibitory*** domains.
Barney, Shawn O'Lin, Cary, NC, United States
Lambert, Dennis Michael, Cary, NC, United States
Petteway, Stephen Robert, Cary, NC, United States
Trimeris, Inc., Durham, NC, United States (U.S. corporation)
US 6020459 20000201
APPLICATION: US 1995-484223 19950607 (8)
DOCUMENT TYPE: Utility.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to peptides which exhibit potent anti-retroviral activity. The peptides of the invention comprise DP178 (SEQ ID:1) peptide corresponding to amino acids 638 to 673 of the ***HIV*** -1.sub.LAI gp41 protein, and fragments, analogs and homologs of DP178. The invention further relates to the uses of such peptides as ***inhibitory*** of human and non-human retroviral, especially ***HIV*** , transmission to uninfected cells.

L16 ANSWER 2 OF 21 MEDLINE
1998087481 Document Number: 98087481. PubMed ID: 9427609. AMD3100, a small molecule inhibitor of HIV-1 entry via the CXCR4 co-receptor. Donzella G A; Schols D; Lin S W; Este J A; Nagashima K A; Maddon P J; ***Allaway G P*** ; Sakmar T P; Henson G; De Clercq E; Moore J P. (The Aaron Diamond AIDS Research Center, The Rockefeller University, New York, New York 10016, USA.) NATURE MEDICINE, (1998 Jan) 4 (1) 72-7. Journal code: CG5; 9502015. ISSN: 1078-8956. Pub. country: United States. Language: English.

AB The bicyclam AMD3100 (formula weight 830) blocks HIV-1 entry and membrane fusion via the CXCR4 co-receptor, but not via CCR5. AMD3100 prevents monoclonal antibody 12G5 from binding to CXCR4, but has no effect on binding of monoclonal antibody 2D7 to CCR5. It also inhibits binding of the CXC-chemokine, SDF-1alpha, to CXCR4 and subsequent signal transduction, but does not itself cause signaling and has no effect on RANTES signaling via CCR5. Thus, AMD3100 prevents CXCR4 functioning as both a HIV-1 co-receptor and a CXC-chemokine receptor. Development of small molecule inhibitors of HIV-1 entry is feasible.

L16 ANSWER 4 OF 21 MEDLINE
97064177 Document Number: 97064177. PubMed ID: 8906796. CD4-dependent, antibody-sensitive interactions between HIV-1 and its co-receptor CCR-5. Trkola A; Dragic T; Arthos J; Binley J M; Olson W C; ***Allaway G P*** ; Cheng-Mayer C; Robinson J; Maddon P J; Moore J P. (The Aaron Diamond AIDS Research Centre, The Rockefeller University, New York 10016, USA.) NATURE, (1996 Nov 14) 384 (6605) 184-7. Journal code: NSC; 0410462. ISSN: 0028-0836. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The beta-chemokine receptor CCR-5 is an essential co-factor for fusion of HIV-1 strains of the non-syncytium-inducing (NSI) phenotype with CD4+ T-cells. The primary binding site for human immunodeficiency virus (HIV)-1 is the CD4 molecule, and the interaction is mediated by the viral surface glycoprotein gp120 (refs 6, 7). The mechanism of CCR-5 function during HIV-1 entry has not been defined, but we have shown previously that its beta-chemokine ligands prevent HIV-1 from fusing with the cell. We therefore investigated whether CCR-5 acts as a second binding site for HIV-1 simultaneously with or subsequent to the interaction between gp120 and CD4. We used a competition assay based on gp120 inhibition of the binding of the CCR-5 ligand, macrophage inflammatory protein (MIP)-1beta, to its receptor on activated CD4+ T cells or CCR-5-positive CD4- cells. We conclude that CD4 binding, although not absolutely necessary for the gp120-CCR-5 interaction, greatly increases its efficiency. Neutralizing monoclonal antibodies against several sites on gp120, including the V3 loop and CD4-induced epitopes, inhibited the interaction of gp120 with CCR-5, without affecting gp120-CD4 binding. Interference with HIV-1 binding to one or both of its receptors (CD4 and CCR-5) may be an important mechanism of virus neutralization.

L16 ANSWER 6 OF 21 MEDLINE
96260018 Document Number: 96260018. PubMed ID: 8649512. HIV-1 entry into CD4+ cells is mediated by the chemokine receptor CC-CKR-5. Dragic T; Litwin V; ***Allaway G P*** ; Martin S R; Huang Y; Nagashima K A; Cayanan C; Maddon P J; Koup R A; Moore J P; Paxton W A. (The Aaron Diamond AIDS Research Center, The Rockefeller University, New York 10016, USA.) NATURE, (1996 Jun 20) 381 (6584) 667-73. Journal code: NSC; 0410462. ISSN: 0028-0836. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The beta-chemokines MIP-1alpha, MIP-1beta and RANTES inhibit infection of CD4+ T cells by primary, non-syncytium-inducing (NSI) HIV-1 strains at the

virus entry stage, and also block env-mediated cell-cell membrane fusion. CD4+ T cells from some HIV-1-exposed uninfected individuals cannot fuse with NSI HIV-1 strains and secrete high levels of beta-chemokines. Expression of the beta-chemokine receptor CC-CKR-5 in CD4+, non-permissive human and non-human cells renders them susceptible to infection by NSI strains, and allows env-mediated membrane fusion. CC-CKR-5 is a second receptor for NSI primary viruses.

L19 ANSWER 4 OF 25 MEDLINE
2000413756 Document Number: 20341767. PubMed ID: 10882617. Single-dose safety, pharmacology, and antiviral activity of the human immunodeficiency virus (HIV) type 1 entry inhibitor PRO 542 in HIV-infected adults. Jacobson J M; Lowy I; Fletcher C V; O'Neill T J; Tran D N; Ketas T J; Trkola A; Klotman M E; ***Maddon P J*** ; Olson W C; Israel R J. (Mount Sinai Medical Center, New York, NY 10029-6574, USA.. jeffrey.jacobson@mssm.edu) . JOURNAL OF INFECTIOUS DISEASES, (2000 Jul) 182 (1) 326-9. Journal code: IH3; 0413675. ISSN: 0022-1899. Pub. country: United States. Language: English.

AB PRO 542 (CD4-IgG2) is a recombinant antibody-like fusion protein wherein the Fv portions of both the heavy and light chains of human IgG2 have been replaced with the D1D2 domains of human CD4. Unlike monovalent and divalent CD4-based proteins, tetravalent PRO 542 potently neutralizes diverse primary human immunodeficiency virus (HIV) type 1 isolates. In this phase 1 study, the first evaluation of this compound in humans, HIV-infected adults were treated with a single intravenous infusion of PRO 542 at doses of 0.2-10 mg/kg. PRO 542 was well tolerated, and no dose-limiting toxicities were identified. Area under the concentration-time curve, and peak serum concentrations increased linearly with dose, and a terminal serum half-life of 3-4 days was observed. No patient developed antibodies to PRO 542. Preliminary evidence of antiviral activity was observed as reductions in both plasma HIV RNA and plasma viremia. Sustained antiviral effects may be achieved with repeat dosing with PRO 542.

L19 ANSWER 8 OF 25 MEDLINE
92296680 Document Number: 92296680. PubMed ID: 1605591. Simple assay to screen for inhibitors of interaction between the human immunodeficiency virus envelope glycoprotein and its cellular receptor, CD4. Chams V; Idziorek T; ***Maddon P J*** ; Klatzmann D. (Laboratoire de Biologie et Genetique des Infections Retrovirales, Groupe Hospitalier Pitie-Salpetriere, URA Centre National de la Recherche Scientifique 1463, Paris, France.) ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, (1992 Feb) 36 (2) 267-72. Journal code: 6HK; 0315061. ISSN: 0066-4804. Pub. country: United States. Language: English.

AB The binding of the human immunodeficiency virus envelope glycoprotein gp120 to the CD4 molecule is the initial step in the viral replicative cycle. This interaction is therefore an important target for therapeutic intervention for the treatment of human immunodeficiency virus infection. We designed an enzyme-linked immunosorbent assay which detects the interaction between recombinant soluble forms of CD4 and gp160. This assay could be used as an initial screen of libraries of synthetic chemical compounds and natural products.

L24 ANSWER 10 OF 10 MEDLINE
97248012 Document Number: 97248012. PubMed ID: 9094135. FP-21399 blocks ***HIV*** envelope protein-mediated membrane fusion and concentrates in lymph nodes. Ono M; Wada Y; Wu Y; Nemori R; Jinbo Y; Wang H; Lo K M; Yamaguchi N; Brunkhorst B; Otomo H; Wesolowski J; Way J C; Itoh I; Gillies S; Chen L B. (Fuji ImmunoPharmaceuticals Corp., Lexington, MA 02173, USA.

) NATURE BIOTECHNOLOGY, (1997 Apr) 15 (4) 343-8. Journal code: CQ3; 9604648. ISSN: 1087-0156. Pub. country: United States. Language: English.

AB The identification of fusin and other ***chemokine*** receptors as coreceptors for ***HIV*** -1 has renewed the interest in agents that may prevent viral entry. Polyanionic compounds such as dextran sulfate, curdian sulfate, and suramin act on the V3 loop of the viral envelope and may prevent its interaction with fusin. These agents show activity against a wide range of ***HIV*** -1 strains, but have undesirable circulating half-life, bioavailability, and toxicity. We have developed a ***small*** ***molecule*** ***inhibitor*** of ***HIV*** -1 that has several advantages over these other agents. FP-21399 is a novel compound of the bis(disulfonaphthalene) dimethoxybenzene class that blocks entry of ***HIV*** into CD4+ cells and blocks fusion of infected and noninfected CD4+ cells. This compound only weakly inhibits binding of CD4 and gp120, at concentrations much greater than are required to block viral entry. Furthermore, FP-21399 can block the interaction between gp120 and antibodies directed against the V3 loop, but does not block binding of antibodies directed against the V4 loop. Animal studies demonstrate that FP-21399 is concentrated in lymph nodes, making it a promising compound for anti- ***HIV*** therapy. In SCID mice reconstituted with human immune cells, maintenance of ***HIV*** -1 infection was blocked by a 5-day treatment with low doses of FP-21399, suggesting that lymph node accumulation may contribute to antiviral activity. Finally, attempts to generate drug-resistant virus in cell culture resulted in only weakly resistant variants with IC90 values that are much lower than concentrations of FP-21399 found in lymph nodes.

L24 ANSWER 9 OF 10 MEDLINE

97477424 Document Number: 97477424. PubMed ID: 9334380. A ***small*** - ***molecule*** ***inhibitor*** directed against the ***chemokine*** receptor ***CXCR4*** prevents its use as an ***HIV*** -1 coreceptor. Doranz B J; Grovit-Ferbas K; Sharron M P; Mao S H; Goetz M B; Daar E S; Doms R W; O'Brien W A. (Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia 19104, USA.) JOURNAL OF EXPERIMENTAL MEDICINE, (1997 Oct 20) 186 (8) 1395-400. Journal code: I2V; 2985109R. ISSN: 0022-1007. Pub. country: United States. Language: English.

AB The ***chemokine*** receptor ***CXCR4*** is the major coreceptor used for cellular entry by T cell- tropic ***human*** ***immunodeficiency*** ***virus*** (***HIV***)-1 strains, whereas ***CCR5*** is used by macrophage (M)-tropic strains. Here we show that a ***small*** - ***molecule*** ***inhibitor*** , ALX40-4C, inhibits ***HIV*** -1 envelope (Env)-mediated membrane fusion and viral entry directly at the level of coreceptor use. ALX40-4C inhibited ***HIV*** -1 use of the coreceptor ***CXCR4*** by T- and dual-tropic ***HIV*** -1 strains, whereas use of ***CCR5*** by M- and dual-tropic strains was not inhibited. Dual-tropic viruses capable of using both ***CXCR4*** and ***CCR5*** were inhibited by ALX40-4C only when cells expressed ***CXCR4*** alone. ALX40-4C blocked stromal-derived factor (SDF)-1alpha-mediated activation of ***CXCR4*** and binding of the monoclonal antibody 12G5 to cells expressing ***CXCR4*** . Overlap of the ALX40-4C binding site with that of 12G5 and SDF implicates direct blocking of Env interactions, rather than downregulation of receptor, as the mechanism of inhibition. Thus, ALX40-4C represents a ***small*** - ***molecule*** ***inhibitor*** of ***HIV*** -1 infection that acts directly against a ***chemokine*** receptor at the level of Env-mediated membrane fusion.

L24 ANSWER 8 OF 10 MEDLINE

1998087481 Document Number: 98087481. PubMed ID: 9427609. AMD3100, a ***small*** ***molecule*** ***inhibitor*** of ***HIV*** -1 entry via the ***CXCR4*** co-receptor. Donzella G A; Schols D; Lin S W; Este J A; Nagashima K A; Maddon P J; Allaway G P; Sakmar T P; Henson G; De Clercq E; Moore J P. (The Aaron Diamond AIDS Research Center, The Rockefeller University, New York, New York 10016, USA.) NATURE MEDICINE, (1998 Jan) 4 (1) 72-7. Journal code: CG5; 9502015. ISSN: 1078-8956. Pub. country: United States. Language: English.

AB The bicyclam AMD3100 (formula weight 830) blocks ***HIV*** -1 entry and membrane fusion via the ***CXCR4*** co-receptor, but not via ***CCR5*** . AMD3100 prevents monoclonal antibody 12G5 from binding to ***CXCR4*** , but has no effect on binding of monoclonal antibody 2D7 to ***CCR5*** . It also inhibits binding of the CXC- ***chemokine*** , SDF-1alpha, to ***CXCR4*** and subsequent signal transduction, but does not itself cause signaling and has no effect on RANTES signaling via ***CCR5*** . Thus, AMD3100 prevents ***CXCR4*** functioning as both a ***HIV*** -1 co-receptor and a CXC- ***chemokine*** receptor. Development of ***small*** ***molecule*** ***inhibitors*** of ***HIV*** -1 entry is feasible.

L24 ANSWER 7 OF 10 MEDLINE
1998328205 Document Number: 98328205. PubMed ID: 9665268. ***Small*** ***molecule*** ***inhibitor*** of ***HIV*** -1 cell fusion blocks ***chemokine*** receptor-mediated function. Howard O M; Korte T; Tarasova N I; Grimm M; Turpin J A; Rice W G; Michejda C J; Blumenthal R; Oppenheim J J. (Intramural Research Support Program, SAIC Frederick, Maryland, USA.. howardz@ncifcrf.gov) . JOURNAL OF LEUKOCYTE BIOLOGY, (1998 Jul) 64 (1) 6-13. Ref: 34. Journal code: IWY; 8405628. ISSN: 0741-5400. Pub. country: United States. Language: English.

AB The intersection of the ***HIV*** and the ***chemokine*** fields began with the observation that ***HIV*** entry into cells could be blocked by certain chemokines. Subsequent work showed that ***HIV*** entry is dependent on the presence of specific ***chemokine*** receptors. These observations led us to evaluate a series of compounds, ureido analogs of distamycin previously reported to block ***HIV*** entry into cells in vitro, for ***chemokine*** antagonist activity. One of the distamycin analogs, 2,2'[4,4'-[[aminocarbonyl]amino]bis[N,4'-di[pyrrole-2-carboxamide- 1,1'-dimethyl]]-6,8 napthalenedisulfonic acid] hexasodium salt (NSC 651016), is shown here to inhibit syncytia formation and cell fusion. Mechanistic studies showed that this inhibition was not due to conformational changes in gp120-gp41 induced by target cell CD4 and ***chemokine*** co-receptor and was therefore not due to interference with binding of ***HIV*** -1. Additional mechanistic studies demonstrated that NSC 651016 inhibited ***chemokine*** binding to specific ***chemokine*** receptors, induced ***CXCR4*** and ***CCR5*** receptor internalization, and inhibited ***chemokine*** -induced chemotaxis by macrophage inflammatory protein (MIP)-1alpha, MIP-1beta, RANTES, and stromal-derived factor-1alpha but not monocyte chemotactic protein-1. Thus, we describe a novel compound that inhibits in vivo replication of ***HIV*** -1 by down-regulation of co-receptors. These data lead us to propose that NSC 651016 may have in vivo anti-inflammatory activity.

L24 ANSWER 6 OF 10 MEDLINE
1999135780 Document Number: 99135780. PubMed ID: 9952309. ***Chemokine*** receptors--future therapeutic targets for ***HIV*** ?. Proudfoot A E; Wells T N; Clapham P R. (Serono Pharmaceutical Research Institute, Geneva, Switzerland.. Amanda.proudfoot@serono.com) . BIOCHEMICAL PHARMACOLOGY, (1999 Mar 1) 57 (5) 451-63. Ref: 123. Journal

code: 9Z4; 0101032. ISSN: 0006-2952. Pub. country: ENGLAND: United Kingdom. Language: English.

AB To date, triple drug therapies for ***HIV*** have resulted in spectacular reductions in the number of virus particles and often remarkable recovery from disease in infected people. There is still, however, a great need for improved therapies. A battery of drugs aimed at different stages in the life cycle of ***HIV*** will enable switching of treatments if resistant viruses emerge or if patients are unable to tolerate particular therapies. Intense efforts are now underway to produce drugs that target ***chemokine*** receptors used by ***HIV*** to gain entry into cells. ***HIV*** needs two receptors on the host cell surface for efficient attachment and infection. ***HIV*** first interacts with CD4 but requires a coreceptor to penetrate the cell membrane. The first coreceptor, identified in 1996, is a member of the family of ***chemokine*** receptors, members of the G-protein coupled 7TM superfamily, which are involved in the trafficking of leukocytes in immune surveillance and inflammation. Such a therapeutic approach would differ from those used successfully to date, which focus largely on proteins coded by the ***HIV*** virus itself, and which are required for the replicative cycle of the virus. Many small, orally bioavailable molecules that block various 7TM receptors are used to treat a panoply of diseases including ulcers, allergies, migraines, and schizophrenia. These molecules are the cornerstone of the pharmaceutical industry's contribution to the fight against so many diseases, and it is hoped that a ***small*** ***molecule*** ***inhibitor*** of coreceptors can be developed that will become an invaluable drug in the fight against AIDS.

L24 ANSWER 4 OF 10 MEDLINE
2000266418 Document Number: 20266418. PubMed ID: 10779565. A binding pocket for a ***small*** ***molecule*** ***inhibitor*** of ***HIV*** -1 entry within the transmembrane helices of ***CCR5*** . Dragic T; Trkola A; Thompson D A; Cormier E G; Kajumo F A; Maxwell E; Lin S W; Ying W; Smith S O; Sakmar T P; Moore J P. (Aaron Diamond AIDS Research Center, The Rockefeller University, New York, NY 10016, USA.. tdragic@aecom.yu.edu) . PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (2000 May 9) 97 (10) 5639-44. Journal code: PV3; 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB ***HIV*** -1 entry into CD4(+) cells requires the sequential interactions of the viral envelope glycoproteins with CD4 and a coreceptor such as the ***chemokine*** receptors ***CCR5*** and ***CXCR4*** . A plausible approach to blocking this process is to use small molecule antagonists of coreceptor function. One such inhibitor has been described for ***CCR5*** : the TAK-779 molecule. To facilitate the further development of entry inhibitors as antiviral drugs, we have explored how TAK-779 acts to prevent ***HIV*** -1 infection, and we have mapped its site of interaction with ***CCR5*** . We find that TAK-779 inhibits ***HIV*** -1 replication at the membrane fusion stage by blocking the interaction of the viral surface glycoprotein gp120 with ***CCR5*** . We could identify no amino acid substitutions within the extracellular domain of ***CCR5*** that affected the antiviral action of TAK-779. However, alanine scanning mutagenesis of the transmembrane domains revealed that the binding site for TAK-779 on ***CCR5*** is located near the extracellular surface of the receptor, within a cavity formed between transmembrane helices 1, 2, 3, and 7.

L24 ANSWER 1 OF 10 MEDLINE
2001176276 Document Number: 21019736. PubMed ID: 11138781. The strategy of blocking the ***chemokine*** system to combat disease. Proudfoot A

E; Power C A; Wells T N. (Serono Pharmaceutical Research Institute, Geneva, Switzerland.. Amanda.Proudfoot@serono.com) . IMMUNOLOGICAL REVIEWS, (2000 Oct) 177 246-56. Ref: 65. Journal code: GG4; 7702118. ISSN: 0105-2896. Pub. country: Denmark. Language: English.

AB One of the key characteristics of inflammation is the recruitment of leukocytes to the site of inflammation. Most anti-inflammatory strategies act intracellularly on the target cells, but after the cells have migrated to the site. We therefore propose that the prevention of cellular recruitment by blockade of the relevant ***chemokine*** receptor/ligand pair would present a novel therapy in that it would act upstream of the therapies currently in use. The ***chemokine*** system is a complex family of over 40 ligands and 18 receptors and as such may appear difficult to inhibit selectively. In the first part of the article we discuss the specificity mechanisms that are beginning to be unraveled which we believe occur at multiple levels. These levels of control of specificity include the temporal regulation of both the ligands and their receptors, which are under the control of pro-inflammatory cytokines; the localization of chemokines on cell surfaces through their interactions with glycosaminoglycans; differential receptor/ligand interactions; and different patterns of receptor trafficking, to name but a few. The ***chemokine*** system has been validated as providing good therapeutic targets by several approaches. In our laboratory, we have used a ***chemokine*** receptor antagonist in models of inflammation in vivo to demonstrate that this approach is successful in reducing inflammation. ***Chemokine*** receptors belong to the class of seven transmembrane spanning receptors, which have proven to be excellent targets by the pharmaceutical industry for many diseases. The number of ***small*** ***molecule*** ***inhibitors*** of ***chemokine*** receptors is rapidly growing in the patent literature, and reports both in the literature as well as conferences in the field have shown them to be effective in inflammatory disease models, as well as inhibiting ***HIV*** -1 infection. Since clinical trials will begin this year with some of these molecules, hopefully we will fairly soon have the answer of the efficacy of this therapeutic approach.

L28 ANSWER 11 OF 11 MEDLINE
1999254104 Document Number: 99254104. PubMed ID: 10318947. A small-molecule, nonpeptide CCR5 antagonist with highly potent and selective anti- ***HIV*** -1 activity. Baba M; Nishimura O; Kanzaki N; Okamoto M; Sawada H; Iizawa Y; Shiraishi M; Aramaki Y; Okonogi K; Ogawa Y; Meguro K; Fujino M. (Division of Human Retroviruses, Center for Chronic Viral Diseases, Faculty of Medicine, Kagoshima University, Kagoshima 890-8520, Japan.) PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1999 May 11) 96 (10) 5698-703. Journal code: PV3; 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB The beta-chemokine receptor CCR5 is considered to be an attractive target for inhibition of macrophage-tropic (CCR5-using or R5) ***HIV*** -1 replication because individuals having a nonfunctional receptor (a homozygous 32-bp deletion in the CCR5 coding region) are apparently normal but resistant to infection with R5 ***HIV*** -1. In this study, we found that ***TAK*** - ***779*** , a nonpeptide compound with a small molecular weight (Mr 531.13), antagonized the binding of RANTES (regulated on activation, normal T cell expressed and secreted) to CCR5-expressing Chinese hamster ovary cells and blocked CCR5-mediated Ca2+ signaling at nanomolar concentrations. The inhibition of beta-chemokine receptors by ***TAK*** - ***779*** appeared to be specific to CCR5 because the compound antagonized CCR2b to a lesser extent but did not affect CCR1, CCR3, or CCR4. Consequently, ***TAK*** - ***779*** displayed highly

potent and selective inhibition of R5 ***HIV*** -1 replication without showing any cytotoxicity to the host cells. The compound inhibited the replication of R5 ***HIV*** -1 clinical isolates as well as a laboratory strain at a concentration of 1.6-3.7 nM in peripheral blood mononuclear cells, though it was totally inactive against T-cell line-tropic (CXCR4-using or X4) ***HIV*** -1.

L28 ANSWER 10 OF 11 MEDLINE
2000192716 Document Number: 20192716. PubMed ID: 10728472. The emerging role of fusion inhibitors in ***HIV*** infection. De Clercq E. (Rega Institute for Medical Research, Katholieke Universiteit Leuven, Belgium.. erik.declercq@rega.kuleuven.ac.be) . DRUGS IN R&D, (1999 Nov) 2 (5) 321-31. Ref: 47. Journal code: DIY; 100883647. ISSN: 1174-5886. Pub. country: New Zealand. Language: English.

AB Fusion of ***HIV*** with its host cell requires the interaction of the viral envelope glycoprotein 120 (gp120) with the chemokine receptor CXCR4 [T cell-tropic (T-tropic) or X4 ***HIV*** strains] or CCR5 [macrophage-tropic (M-tropic) or R5 ***HIV*** strains] followed by a 'spring-loaded' action of the glycoprotein 41 (gp41) that ensures fusion of the viral and cellular lipid membranes and permits the viral nucleocapsid to enter the cell. The overall fusion process can be blocked by a number of compounds. These include siamycin analogues, SPC 3 (a synthetic peptide derived from the V3 domain of gp120), pentafuside (T 20, DP 178) [a synthetic peptide corresponding to amino acid residues 127 to 162 of gp41], the betulinic acid derivative RPR 103611, ***TAK*** ***779*** (a low molecular weight non-peptide CCR5 antagonist) and a number of compounds (T 22, T 134, ALX40-4C, CGP64222 and AMD 3100) that are targeted at the CXCR4 receptor. In particular, the bicyclam AMD 3100 has proved highly potent and selective as a CXCR4 antagonist that blocks the infectivity of X4 ***HIV*** strains in the nanomolar concentration range. The proof-of-concept that fusion inhibitors should be able to suppress viral replication in vivo has been demonstrated with pentafuside. Pentafuside and AMD 3100 have now proceeded to phase II clinical trials.

L28 ANSWER 6 OF 11 MEDLINE
2000411063 Document Number: 20351801. PubMed ID: 10891872. Novel compounds in preclinical/early clinical development for the treatment of ***HIV*** infections. De Clercq E. (Rega Institute for Medical Research, Katholieke Universiteit Leuven, Belgium.) REVIEWS IN MEDICAL VIROLOGY, (2000 Jul-Aug) 10 (4) 255-77. Ref: 165. Journal code: DET; 9112448. ISSN: 1052-9276. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Virtually all the compounds that are currently used, or under advanced clinical trial, for the treatment of ***HIV*** infections, belong to one of the following classes: (i) nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), (ii) non-nucleoside reverse transcriptase inhibitors (NNRTIs) and (iii) protease inhibitors (PIs). In addition to the reverse transcriptase and protease step, various other events in the ***HIV*** replicative cycle are potential targets for chemotherapeutic intervention: (i) viral adsorption, through binding to the viral envelope glycoprotein gp120 (polysulphates, polysulphonates, polyoxometalates, zintevir, negatively charged albumins); (ii) viral entry, through blockade of the viral coreceptors CXCR4 and CCR5 [bicyclams (AMD3100), polyphemusins (T22), ***TAK*** - ***779***]; (iii) virus-cell fusion, through binding to the viral glycoprotein gp41 [T-20 (DP-178), siamycins, betulinic acid derivatives]; (iv) viral assembly and disassembly, through NCp7 zinc finger-targeted agents [2,2'-dithiobisbenzamides (DIBAs), azadicarbonamide (ADA)]; (v) proviral DNA integration, through integrase inhibitors such as L-chicoric acid; (vi) viral mRNA transcription, through inhibitors of the transcription

(transactivation) process (peptoid CGP64222, fluoroquinolone K-12, Streptomyces product EM2487). Also, in recent years new NRTIs, NNRTIs and PIs have been developed that possess, respectively, improved metabolic characteristics (i.e. phosphoramidate and cyclosaligenyl pronucleotides of d4T), or increased activity against NNRTI-resistant ***HIV*** strains, or, in the case of PIs, a different, non-peptidic scaffold. Given the multitude of molecular targets with which anti- ***HIV*** agents can interact, one should be cautious in extrapolating from cell-free enzymatic assays to the mode of action of these agents in intact cells. A number of compounds (i.e. zintevir and L-chicoric acid, on the one hand; and CGP64222 on the other hand) have recently been found to interact with virus-cell binding and viral entry in contrast to their proposed modes of action targeted at the integrase and transactivation process, respectively.

L29 ANSWER 10 OF 15 MEDLINE
97477424 Document Number: 97477424. PubMed ID: 9334380. A small-molecule inhibitor directed against the chemokine receptor CXCR4 prevents its use as an ***HIV*** -1 coreceptor. Doranz B J; Grovit-Ferbas K; Sharron M P; Mao S H; Goetz M B; Daar E S; Doms R W; O'Brien W A. (Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia 19104, USA.) JOURNAL OF EXPERIMENTAL MEDICINE, (1997 Oct 20) 186 (8) 1395-400. Journal code: I2V; 2985109R. ISSN: 0022-1007. Pub. country: United States. Language: English.

AB The chemokine receptor CXCR4 is the major coreceptor used for cellular entry by T cell- tropic ***human*** ***immunodeficiency*** ***virus*** (***HIV***)-1 strains, whereas CCR5 is used by macrophage (M)-tropic strains. Here we show that a small-molecule inhibitor, ***ALX40*** - ***4C*** , inhibits ***HIV*** -1 envelope (Env)-mediated membrane fusion and viral entry directly at the level of coreceptor use. ***ALX40*** - ***4C*** inhibited ***HIV*** -1 use of the coreceptor CXCR4 by T- and dual-tropic ***HIV*** -1 strains, whereas use of CCR5 by M- and dual-tropic strains was not inhibited. Dual-tropic viruses capable of using both CXCR4 and CCR5 were inhibited by ***ALX40*** - ***4C*** only when cells expressed CXCR4 alone. ***ALX40*** - ***4C*** blocked stromal-derived factor (SDF)-1alpha-mediated activation of CXCR4 and binding of the monoclonal antibody 12G5 to cells expressing CXCR4. Overlap of the ***ALX40*** - ***4C*** binding site with that of 12G5 and SDF implicates direct blocking of Env interactions, rather than downregulation of receptor, as the mechanism of inhibition. Thus, ***ALX40*** - ***4C*** represents a small-molecule inhibitor of ***HIV*** -1 infection that acts directly against a chemokine receptor at the level of Env-mediated membrane fusion.

L33 ANSWER 59 OF 61 MEDLINE
97248644 Document Number: 97248644. PubMed ID: 9092481. Potent inhibition of ***HIV*** -1 ***infectivity*** in macrophages and lymphocytes by a novel ***CCR5*** ***antagonist*** . Simmons G; Clapham P R; Picard L; Offord R E; Rosenkilde M M; Schwartz T W; Buser R; Wells T N; Proudfoot A E. (Virology Group, Chester Beatty Laboratories, Institute of Cancer Research, 237 Fulham Road, London SW3 6JB, UK.) SCIENCE, (1997 Apr 11) 276 (5310) 276-9. Journal code: UJ7; 0404511. ISSN: 0036-8075. Pub. country: United States. Language: English.

AB The ***chemokine*** receptors ***CXCR4*** and ***CCR5*** have recently been shown to act as coreceptors, in concert with CD4, for ***human*** ***immunodeficiency*** ***virus*** -type 1 (***HIV*** -1) infection. RANTES and other chemokines that interact with ***CCR5*** and block infection of peripheral blood mononuclear cell

cultures inhibit infection of primary macrophages inefficiently at best. If used to treat ***HIV*** -1-infected individuals, these chemokines could fail to influence ***HIV*** replication in nonlymphocyte compartments while promoting unwanted inflammatory side effects. A derivative of RANTES that was created by chemical modification of the amino terminus, aminooxypentane (AOP)-RANTES, did not induce chemotaxis and was a subnanomolar ***antagonist*** of ***CCR5*** function in monocytes. It potently inhibited infection of diverse cell types (including macrophages and lymphocytes) by nonsyncytium-inducing, macrophage-tropic ***HIV*** -1 strains. Thus, activation of cells by chemokines is not a prerequisite for the inhibition of viral uptake and replication. ***Chemokine*** receptor antagonists like AOP-RANTES that achieve full receptor occupancy at nanomolar concentrations are strong candidates for the therapy of ***HIV*** -1-infected individuals.

L34 ANSWER 2 OF 13 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 2000-571320 [53] WPIDS
CR 1999-080861 [07]
DNC C2000-170238
TI Determining an agent capable of inhibiting HIV-1 infection of a susceptible CD4+ cell comprises contacting a chemokine receptor and gp120/CD4+ complex in presence and absence of the agent and comparing them.
DC B04 D16
IN ***ALLAWAY, G P*** ; LITWIN, V M; MADDON, P J; OLSON, W C
PA (PROG-N) PROGENICS PHARM INC
CYC 1
PI US 6107019 A 20000822 (200053)* 26p
ADT US 6107019 A Provisional US 1996-14532 19960402, Provisional US 1996-19715 19960614, CIP of US 1997-831823 19970402, US 1997-876078 19970613
PRAI US 1997-876078 19970613; US 1996-14532 19960402; US 1996-19715 19960614; US 1997-831823 19970402

AB US 6107019 A UPAB: 20001023
NOVELTY - A chemokine receptor (I) which is a co-receptor for HIV-1 infection, fixed to a solid matrix is contacted with a candidate agent (C) and the resulting fixed (I) to which (C) is bound is contacted with defined amount of gp120/CD4+ complex (II) in the absence of (C). The amount of (II) bound to fixed (I) is measured and compared with amount measured in absence of (C).
USE - To determine an agent capable of inhibiting HIV-1 infection of a CD4+ cell susceptible to the infection (claimed).
Dwg.0/7

L34 ANSWER 4 OF 13 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1999-080861 [07] WPIDS
CR 2000-571320 [49]
DNN N1999-058161 DNC C1999-024231
TI New non-chemokine agents that inhibit infection by HIV - by binding to chemokine receptors.
DC A96 B04 D16 S03
IN ***ALLAWAY, G P*** ; LITWIN, V M; MADDON, P J; OLSON, W C
PA (PROG-N) PROGENICS PHARM INC
CYC 24
PI WO 9856421 A1 19981217 (199907)* EN 85p
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: AU CA JP MX US
AU 9881426 A 19981230 (199920)
EP 1009435 A1 20000621 (200033) EN
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
ADT WO 9856421 A1 WO 1998-US12331 19980612; AU 9881426 A AU 1998-81426 19980612; EP 1009435 A1 EP 1998-931261 19980612, WO 1998-US12331 19980612
FDT AU 9881426 A Based on WO 9856421; EP 1009435 A1 Based on WO 9856421
PRAI US 1997-876078 19970613

AB WO 9856421 A UPAB: 20001027
A non-chemokine agent (I) that binds to a chemokine receptor (CR) and inhibits fusion of human immune deficiency virus-1 (HIV-1) to CD4+ cells, other than a known bicyclam or its known derivatives, is new.
Also new are: (1) non-chemokine agents (Ia) that bind to CXCR4 and inhibit HIV-1 infection, other than those specified above; (2) composition (A), able to bind to CR and inhibit HIV-1/CD4+ cell fusion, comprising a non-chemokine agent (II) linked to a ligand (L) that binds a receptor on the surface of the CD4 cell, other than CR, such that binding of (II) to CR does not inhibit binding of (L) to its receptor; (3) method for

identifying agents that inhibit HIV-1 infection; and (4) new agents (B) identified this way.

USE - (I), (Ia), (A) and (B) are used to reduce the likelihood of infection by HIV and to treat such infections.

ADVANTAGE - (I) etc. inhibit membrane fusion mediated by HIV-1 envelope protein, resulting in neutralisation of the virus but without inducing an inflammatory response (since they lack the biological activity of chemokines).

Dwg.0/9

L34 ANSWER 6 OF 13 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1998-086550 [08] WPIDS
CR 1998-086551 [05]
DNC C1998-029218
TI Chemokine receptor CCR5 fragments - useful for inhibition of Human Immunodeficiency Virus 1 infection.
DC B04 D16
IN ***ALLAWAY, G P*** ; DRAGIC, T; LITWIN, V M; MADDON, P J; MOORE, J P; TRKOLA, A
PA (AARO-N) AARON DIAMOND AIDS RES CENT; (PROG-N) PROGENICS PHARM INC
CYC 21
PI WO 9747318 A1 19971218 (199808)* EN 86p
RW: AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: AU CA JP MX
AU 9733902 A 19980107 (199820)
ADT WO 9747318 A1 WO 1997-US10233 19970613; AU 9733902 A AU 1997-33902 19970613
FDT AU 9733902 A Based on WO 9747318
PRAI US 1996-665090 19960614; US 1996-19941 19960614

AB WO 9747318 A UPAB: 19980309
The following are claimed: (A) a polypeptide having a sequence corresponding to the sequence of a portion of a chemokine receptor, especially CCR5, and capable of inhibiting the fusion of Human Immunodeficiency Virus (HIV)-1 to CD4+ cells and thus of inhibiting HIV-1 infection of the cells, and (B) a polypeptide having a sequence corresponding to that of a portion of a HIV-1 envelope glycoprotein capable of specifically binding to the chemokine receptor CCR5. Also claimed are: (1) an antibody (Ab) or a portion of an Ab, capable of binding to a chemokine receptor on a CD4+ cell and inhibiting HIV-1 infection of the cell; (2) a non-chemokine agent (C) capable of binding to CCR5 and inhibiting the fusion of HIV-1 to CD4+ cells; (3) a transgenic non-human animal which comprises an isolated DNA molecule encoding CCR5, and optionally an isolated DNA molecule encoding fusion, and (4) a transformed cell which comprises an isolated nucleic acid molecule encoding CCR5.

USE - Polypeptides (A) and (B), which comprise gp120 are useful to inhibit the fusion of HIV-1 to CD4+ cells, this is useful in treatment of an HIV-1 infected subject. The Ab and (C) are also useful for inhibition of HIV-1 infection of CD4+= cells. (A) and (B) are also useful for reducing the likelihood of a subject from becoming infected by HIV-1 by